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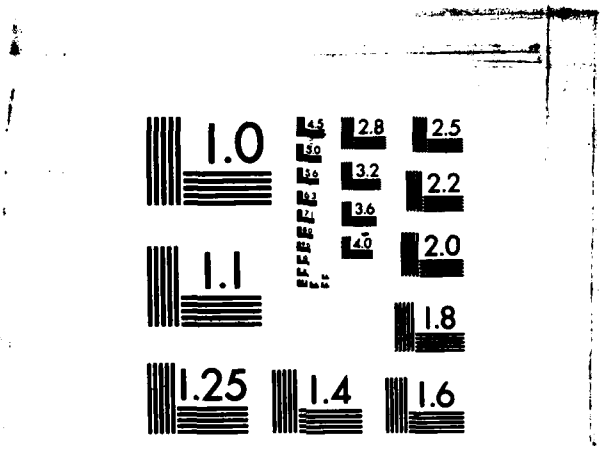

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Final Technical Report (5/1/82-4/30/83)
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Actions of Opioid Peptides on Learning and Memory
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The primary focus of the past year's research has been on the modulatory role of peripheral hormonal systems in influencing learning. Initially we characterized the actions of the opioid agonists Leu-enkephalin and Met-enkephalin on a discriminated Y-maze escape task in mice. Leu-enkephalin was found to impair and Met-enkephalin to enhance acquisition of the response at equivalent doses (100 µg/kg, i.p.). Naloxone (1.0 and 10.0 mg/kg) also enhanced acquisition of the escape response, and blocked the impairing actions of Leu-enkephalin. Neither naloxone nor the enkephalins influenced shock-induced locomotor activity in an open field. The results suggest that enkephalin actions on escape conditioning are mediated through opioid receptors. In a related study we determined whether two forms of naloxonium (chloride and bromide salts), which have a limited ability to cross the blood brain barrier, would affect escape conditioning in a manner similar to naloxone, which crosses freely into the brain. Both forms of naloxonium facilitated acquisition of the response at doses (1.0 mg/kg, i.p.) equivalent to a facilitatory dose of naloxone. Since the naloxoniums do not readily cross into the brain, it is probable that their actions are mediated through peripheral opioid receptors.

It is also likely that Leu-enkephalin affects conditioning by an action at peripheral opioid receptors, since in another study in rats we found that direct intracerebroventricular administration of Leu-enkephalin, at doses up to those that are effective when given peripherally (2.75 µg/rat), do not affect acquisition of an active avoidance response. However, Leu-enkephalin given directly into the brain clearly affected other behaviors such as locomotor activity and shock sensitivity.

In the final series of Leu-enkephalin studies conducted this year it was found that this peptide produces long term effects on one-way active avoidance conditioning in the mouse. In this study 4 trials were run on Day 1, 24 trials on Day 2, and 15 trials were run on Day 5. Leu-enkephalin (200 µg/kg, i.p.) was administered either

following the 4 trials of training on Day 1 or immediately before the 24 trials of training on Day 2. In both cases the Leu-enkephalin impaired avoidance responding on Day 2, and the effect was still evident on Day 5. Thus, Leu-enkephalin may be said to affect acquisition (pre-training administration) and consolidation (post-training administration) of the response. These results are particularly intriguing since the half life of Leu-enkephalin in plasma is about 5 min. Thus, the Leu-enkephalin must be activating a biological system, the nature of which is unknown at the present time.

Other collaborative research on the role of hormones and learning was also completed. In collaboration with G. Koob and F.E. Bloom of the Salk Institute, it was found that the memory enhancing actions of vasopressin on passive avoidance responding were reversed by a vasopressin antagonist [1 deaminopenicillamine-2-(O-methyl) tyrosine arginine vasopressin] [dpTyr (Me)AVP]. Since dpTyr (Me)AVP is known to block the cardiovascular pressor actions of vasopressin, these results suggest that the memory enhancing effects of vasopressin may also be mediated by some peripheral action.

Finally, in collaboration with H. Rigter of Organon International, the Netherlands and A. Oscos of the Centro de Investigación y de Estudias Avanzados del Polytechnico Nacional, Mexico it was found that hexamethonium, a cholinergic nicotinic agonist with a limited ability to cross the blood brain barrier, induces a conditioned taste aversion to glucose water and blocks the amnesia produed by electrical stimulation of the amygdala for a passive avoidance response. These studies emphasize the importance of peripheral autonomic systems in affecting learning in a variety of conditioning situations.

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